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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,180	06/09/1999	TORU KIMURA	20-4546P	1992

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	28

DATE MAILED: 08/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/284,180	Applicant(s) KIMURA ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspond nc addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,41,42 and 48-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *34* is/are allowed.

6)☒ Claim(s) *41,42 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 6-14-02 has been entered. Claims 43, 45 and 54 have been canceled. Claims 41, 42, 48, 51 and 52 have been amended. Claims 34, 41, 42 and 48-52 are pending and under consideration.

Claim Objections

1. The incorporation of essential material in claim 51 by reference to GenBank Accession Nos. T09073 and R54387 is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application at the time of filing. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 51 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "at least 27 contiguous nucleotides disclosed in GenBank Accession No:T09073 or GenBank Accession No:R54387" in claim 51 is vague and renders the claim indefinite. The nucleotide sequences of GenBank Accession No:T09073 and GenBank Accession No:R54387 could be changed with time, it is unclear what nucleotide sequences of GenBank Accession No:T09073 and GenBank Accession No:R54387 are intended in the claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 41, 42 and 48-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on an isolated nucleic acid comprising a complement of a polynucleotide that specifically hybridizes with SEQ ID No. 1 or SEQ ID No. 2 under the hybridization and washing conditions cited in the claims and encodes a protein having the biological activity of

inhibiting neurite outgrowth from dorsal root ganglion cells or collapsing growth cones of retinal ganglion cells, an expression plasmid comprising said nucleic acid, a host cell comprising said expression plasmid, and a process for producing a recombinant protein by using said host cell.

The washing condition, i.e. 2XSSPE at 42°C, recited in the claims is low stringency condition, therefore, the nucleic acid that hybridizes with SEQ ID No. 1 or 2 under the cited washing condition only requires low level of homology to SEQ ID No. 1 or 2 and could vary dramatically from the sequence of SEQ ID Nos. 1 and 2. The claims encompass various nucleic acids having unknown nucleotide sequences adding to 5', 3' and/or within the sequence of SEQ ID No. 1 or 2. The specification of the present application only disclosed the nucleotide sequences of SEQ ID Nos. 1 and 2 (rat semaphorin) and the amino acid sequence deduced from SEQ ID No. 2 (SEQ ID No. 3), and the nucleotide sequences of human semaphorin cDNA (SEQ ID Nos. 4, 5, 7 and 10).

The scope of the claims includes various unknown and unidentified nucleic acids encoding a genus of numerous structural variants of the disclosed semaphorin protein (SEQ ID No. 3) and having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion cells or collapsing growth cones of retinal ganglion cells, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification only discloses the homologies of the primary amino acid sequences in semaphorin domain among the known semaphorin genes are 20-80% and not necessarily high (specification, page 4, lines 17-20), and suggest that the amino acid residue at position 204 of SEQ ID No. 3

could be essential to the activity of semaphorin protein (specification, page 18, lines 17-22). The post-filing documents accompanied with the preliminary amendment filed 11-20-01 indicates that the full length human semaphorin cDNA sequence is 82.4% identical to the rat semaphorin cDNA sequence and the overall degree of amino acid sequence identity is 90.6%. The nucleotide sequence of SEQ ID Nos. 1 and 2 contains 4008 bases and 2331 bases, respectively, and the nucleic acid that hybridizes with SEQ ID No. 1 or 2 under the cited washing condition could be less than 80% identity to SEQ ID No. 1 or 2. The claimed nucleic acids could vary dramatically from the disclosed nucleotide sequences of the present application. Although the human semaphorin cDNA is 82.4% identical to rat semaphorin W cDNA and the method for making variant nucleic acids and assays for identifying protein having the claimed biological activity were known in the art, the scope of the claims encompasses unknown and unidentified genes having nucleotide sequence that is drastically different from the sequence of SEQ ID No. 1 or 2 but do not have the claimed biological activity. The specification fails to provide sufficient description that applicants had possession of the full scope of the nucleic acids at the time of the invention.

Further, as discussed in the preceding Official action mailed 5-24-01 (Paper No. 21), the specification indicates the ""semaphorin domain" refers to a domain consisting of 300-600 amino acid residues more than 20% of which are identical to those amino acids constituting the semaphorin domain of any one of ten known semaphorins" and thirteen cysteines are conserved in semaphorin domain of the ten known semaphorins (Specification, page 23, lines 10-13 and 22-

24). The amino acid sequences between semaphorin domains of the known semaphorins could differ from 240-480 amino acid residues which account to 720-1440 nucleotide difference among the known semaphorin domains. The identical amino acid residues among semaphorin domains of the known semaphorin are not necessarily identical throughout all known semaphorin rather they are identical to a certain subgroups of the known semaphorins. No common structural feature of the nucleic acids that encode the semaphorin domain has been disclosed in the specification except the consensus cysteine residues. Thus, one skilled in the art at the time of the invention would not know how to distinguish the nucleic acid encoding semaphorin protein from the nucleic acid encoding other proteins. This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of all the nucleic acids encoding variants of the semaphorin W disclosed in the present invention. Thus it is concluded that the written description requirement is not satisfied for the nucleic acids that encode the genus of proteins discussed above.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed SEQ ID Nos. 1-3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

6. Claims 41, 42 and 48-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA comprising SEQ ID No. 1 or 2 and a DNA encoding a polypeptide sequence of SEQ ID No. 3 that functions to inhibit neurite outgrowth, does not reasonably provide enablement for any isolated nucleic acid comprising a

complement of a polynucleotide that specifically hybridizes with SEQ ID No. 1 or SEQ ID No. 2 under the hybridization and washing conditions cited in the claims and encodes a protein having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion cells or collapsing growth cones of retinal ganglion cells, an expression plasmid comprising said nucleic acid, a host cell comprising said expression plasmid, and a process for producing a recombinant protein by using said host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to an isolated nucleic acid comprising a complement of a polynucleotide that specifically hybridizes with SEQ ID No. 1 or SEQ ID No. 2 under the hybridization and washing conditions cited in the claims and encodes a protein having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion cells or collapsing growth cones of retinal ganglion cells, an expression plasmid comprising said nucleic acid, a host cell comprising said expression plasmid, and a process for producing a recombinant protein by using said host cell.

As discussed above, the washing condition, i.e. 2XSSPE at 42°C, recited in the claims is low stringency condition, therefore, the nucleic acid that hybridizes with SEQ ID No. 1 or 2 under the cited washing condition only requires low level of homology, e.g. less than 80% identity, to SEQ ID No. 1 or 2 and could vary dramatically from the sequence of SEQ ID Nos. 1 and 2. The claims encompass various nucleic acids having unknown nucleotide sequences

adding to 5', 3' and/or within the sequence of SEQ ID No. 1 or 2. The specification of the present application only disclosed the nucleotide sequences of SEQ ID Nos. 1 and 2 (rat semaphorin) and the amino acid sequence deduced from SEQ ID No. 2 (SEQ ID No. 3), and the nucleotide sequences of human semaphorin cDNA (SEQ ID Nos. 4, 5, 7 and 10).

The scope of the claims include various unknown and unidentified nucleic acids encoding a genus of numerous structural variants, derived from different organisms including humans, cows, dogs, mice, whales, fish, insects, plants etc., of the disclosed semaphorin protein (SEQ ID No. 3), and the genus is highly variant because a significant number of structural differences between genus members is permitted. Nucleotide sequence of SEQ ID Nos. 1 and 2 contains 4008 bases and 2331 bases, respectively, and the nucleic acid that hybridizes with SEQ ID No. 1 or 2 under the cited washing condition could be less than 80% identity to SEQ ID No. 1 or 2 and account for more than 800 bases and 466 bases differences, respectively. The claimed nucleic acids could vary dramatically from the disclosed nucleotide sequences of the present application and the amino acid sequences encoded by said nucleic acid also could vary dramatically.

The specification fails to provide adequate guidance for a domain or a region within a semaphorin that contributes to any functional characteristic of the semaphorin having the sequence of SEQ ID No. 3 other than the proposed amino acid residue at position 204 of SEQ ID No. 3 and somaphorin domain. There is no indication of regions or specific amino acids within the semaphorin where mutations or variations would be tolerated without any change of the

functional characteristic of the semaphorin and regions where they would not be tolerated other than the proposed amino acid residue at position 204 of SEQ ID No. 3. The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (W) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, one skilled in the art at the time of the invention would not be able to predict the function of a protein merely from the amino acid

sequence of said protein. In view of such, the unpredictability of the biological function of a protein, and the lack of detailed information regarding the structural and functional requirements of a semaphorin, it would be unpredictable at the time of the invention whether the proteins encoded by the claimed nucleic acids would still retain the functional characteristic of the amino acid sequence of SEQ ID No. 3.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that one skilled in the art at the time of the invention would have had to engage in undue experimentation to practice over the full scope of the invention claimed.

Conclusion

Claims 41, 42 and 48-52 are rejected. Claim 34 is in condition for allowance..

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.